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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/859,722	SOMERS ET AL.	
	Examiner	Art Unit	
	Suzanne M. Noakes, Ph.D.	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15,16 and 36-69* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15,16 and 36-69* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 25 May 2007 has been entered.

Status of the Application

2. The response to the previous Office action and amendments to the claims filed 25 May 2007 are acknowledged. Applicants have added new claims 61-69, thus, claims 15, 16 and 36-69 are pending and subject to examination.

Withdrawal of Rejections/Objections

3. Any rejection/objection recited in the previous Office action and not explicitly restated below is hereby withdrawn.

Claim Rejections - 35 USC § 112 – 1st paragraph

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Scope of Enablement:

5. Claims 15, 16, 36-60 and new claims 61-69 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for identifying an agent that interacts with P-selectin LE by providing a crystal consisting of P-selectin LE selected from the group consisting of: a) a P-selectin LE crystal of a P-selectin EGF/lectin binding domain consisting of SEQ ID No: 6 and having space group $P2_1$ with unit cell parameters of a=81.0 Å, b= 60.8 Å, c=91.4Å and β=103.6°; b) a P-selectin LE co-crystal of a P-selectin EGF/lectin binding domain consisting of SEQ ID No: 6 complexed with SLe^x and having space group $P2_1$ with unit cell parameters of a=81.1 Å, b= 60.5 Å, c=91.4Å and β=103.3°; and c) a P-selectin LE co-crystal of a P-selectin EGF/lectin binding domain consisting of SEQ ID No: 8 complexed with PSGL-1 (SEQ ID No: 10) and having space group I222 with unit cell parameters of a=63.4 Å, b= 96.8 Å and c=187.3Å; determining the structural coordinates of said crystals and generating 3-D models therefrom of P-selectin LE having the structural coordinates of Figure 2, 3 or 5 ± 0.5-1.5 Å and employing said 3-D structure to design or select an agent that interact with said P-selectin LE, does not reasonably provide enablement for the method which uses any P-selectin LE crystal, which, when the phrase "an amino acid sequence of SEQ ID No: 6, 8 or 9" is broadly interpreted, encompasses *any* P-selectin LE that comprises as few as two consecutive amino acids of SEQ ID No: 6, 8 or 9, or those with conservative substitutions thereof, and which further can form in any of the 65 space groups with corresponding unit cell parameters. The specification does not enable any person skilled in the art to which it pertains, or with which it is most

nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are drawn to *in silico* methods of identifying agents that interact with a P-selectin lectin and EGF (LE) domains wherein said method provides a crystal comprising a P-selectin LE having as few as two contiguous amino acids of SEQ ID No: 6, 8 or 9, or any of these with conservative amino acid substitutions. Thus, the claim is unlimited in the number and variance of different P-selectin LE crystals that can be used in the claims because the protein within the crystal is not limited to any particular P-selectin protein as many different substitutions can be made. Furthermore, "a crystal comprising a P-selectin LE" has been interpreted as encompassing any ligand bound to P-selectin LE of the crystal. In addition, any of these variable P-selectin proteins can then form in any of the 65 space groups with different unit cell parameters. However, the specification only discloses three working examples of protein crystals that fall within the scope of the claims and which are described in the specification on pp. 31-32. For instance, P-selectin LE apo-form, was crystallized at 18°C from a solution containing 10 mg/ml prteoin, 100 mM Tris-HCL (pH 8.5), 150 mM NaCl, 12 mM $CaCl_2$, 10% (v/v) MPD and 10% (w/v) Peg 6k. The transfer solutions necessary for flash-cooling are also described. This kind of detail is necessary and enables one of ordinary skill in the art to reproduce said crystals. However, the countless other crystals which fall within the scope of the claims are not disclosed nor even contemplated in the specification. Because of the extreme unpredictability of crystallizing any protein, even those that have been described previously, the scope of the claims exceed that which is enabled

and a skilled artisan would expected to have to determine, or try to determine *de novo* crystallization conditions in order to make and/or use the claimed invention. In this case, the burden is seen as undue when the Wands analysis is considered.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The Court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

In order to make the protein crystals encompassed by the scope of the claims, the following must be clear: (a) the preparation and chemical composition of the molecules to be crystallized (recited unambiguously) and (b) the crystallization

conditions, including methods and reagents used. Applicants have met this burden for three P-selectin LE crystals in the specification (described on pp. 31-32); however, as stated *supra*, the claims encompass a large number of different protein crystals which have not been described and are by no means trivial to produce. Undue experimentation would be expected in the instant case because even the smallest change in any parameter in crystallizing a protein can have enormous consequences. McPherson (Eur. J. Biochem. 1990, 189:1-23 – cited previously) outlines 25 different parameters which do or could affect crystallization (see Table 2, p. 13). It is stated (p. 13, 2nd column, *Factors influencing protein crystal growth*):

> Table 2 lists physical, chemical and biological variables that may influence to a greater or lesser extent the crystallization of proteins. The difficulty in properly arriving at a just assignment of importance for each factor is substantial for several reasons. *Every protein is different in its properties and, surprisingly perhaps, this applies even to proteins that differ by no more than one or just a few amino acids*. There are even cases where the identical protein prepared by difference procedures or at different times may show significant variations. In addition, each factor may differ considerably in importance for individual proteins.

Thus, it is not enough to have the crystallization conditions of a "native" protein. Rather, what would be required is precise instructions about how to make each and every protein crystal in order to avoid undue experimentation (e.g. conditions for each and P-selectin LE crystal produced with P-selectin protein from any species and which may be derivatives, homologues or fragments thereof). However, there is no direction or guidance in the specification above or beyond the description of the P-selectin LE crystals from humans and the details of a different protein all together E-selectin as disclosed at pp. 31-32 of the specification. The nature of the invention and of the prior

art suggests that crystallizing proteins is an extremely tenuous science; what works for one protein does not necessarily for another, and what works for one native protein does not necessarily work for a mutant or a protein complex and vice-versa which may even contain the same protein that has already been crystallized. Specific crystallization conditions (e.g. temperature, buffer, salt, protein concentration etc.) are needed for each protein (or protein) complex (see also Weber, Methods in Enzymology, 1997, Vol. 276, pp. 13-22 – cited previously). At best, the art of crystallization is unpredictable even to those skilled in the art who may either perform the experiments by hand or who are assisted by automated robotics because it often times requires thousands of individual experiments in order to find the one or two conditions that are successful. Even then, there is no guarantee. It is even a well known fact in the art that luck often times plays a role in obtaining crystallization conditions despite the extremely high skill level of those in the art (see Drenth, "Principles of Protein X-Ray Crystallography", 2nd Edition, 1999 Springer-Verlag New York Inc., Chapter 1, p. 19, 4th paragraph, lines 1-2 - cited previously; and Cudney, Rigaku Journal, 1999, Vol. 16, No. 1, pp. 1-7 – cited previously). Furthermore, the prior art regarding crystallization of P-selectins is of limited assistance because there are no P-selectin proteins from human or other species that are crystallized in the apo form or in complex form.

It is further noted, that even though new claims 61-65 attempt to limit claim 15 or 56 by reciting the specific space group and unit cell parameters (claims 61, 63 and 65), or the ligand of the crystals (claims 62 and 64), this is still deemed beyond the scope of enablement because the independent claims are unlimited as to the amino acid

sequences used to make said crystals, e.g. the claims encompass any P-selectin LE protein comprising as few as two contiguous amino acids of SEQ ID Nos: 6, 8 or 9 and further comprises those proteins with conservative substitutions. As noted above, McPherson expressly states that those proteins that have only one or two substitutions in them can have enormous consequences as to whether or not said proteins will crystallize or crystallize in the same.

However, since the claims currently are broader than what they are enabled for, when all things are considered and the Wands factors are treated on their merits, the claims are not enabled because a great deal of undue experimentation would be expected and necessary in order to practice the claimed invention.

Written Description:

6. Claims 15, 16, 36-60 and new claims 61-69 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The claims are drawn to *in silico* methods of identifying agents that interact with a P-selectin lectin and EGF (LE) domains wherein said method provides a crystal comprising a P-selectin LE comprising as few as two contiguous amino acids of SEQ ID Nos: 6, 8 or 9, or those with conservative substitutions thereof. Thus, the claims are intrinsically drawn to large number of species of P-selectin crystals containing a considerable number of different P-selectin proteins and thus the claims possess a

large genus of widely variant crystals of both P-selecting proteins used to make the crystals, as well as a large genus of widely variant crystal forms themselves (e.g. any of the 65 space groups). Also, as noted above, the crystal can have any ligand bound to the P-selectin LE. However, the specification only adequately describes three representative species in terms of both structure and function which belong to this genus.

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." University of California v. Eli Lilly and Co., 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these (Enzo Biochem 63 USPQ2d 1609 (CAFC 2002)).

The specification fully describes three representative species of a P-selectin LE crystals that fall within the instant genera of crystals, those being: a) a P-selectin LE

crystal of a P-selectin EGF/lectin binding domain consisting of SEQ ID No: 6 and having space group $P2_1$ with unit cell parameters of a=81.0 Å, b= 60.8 Å, c=91.4Å and β=103.6°; b) a P-selectin LE co-crystal of a P-selectin EGF/lectin binding domain consisting of SEQ ID No: 6 complexed with SLe^x and having space group $P2_1$ with unit cell parameters of a=81.1 Å, b= 60.5 Å, c=91.4Å and β=103.3°; and c) a P-selectin LE co-crystal of a P-selectin EGF/lectin binding domain consisting of SEQ ID No: 8 complexed with PSGL-1 (SEQ ID No: 10) and having space group I222 with unit cell parameters of a=63.4 Å, b= 96.8 Å and c=187.3Å. These particular crystals are the only species representative of the genus based upon the description of the proteins that make up the crystal (e.g. SEQ ID No:), and the characteristics of the crystal itself, e.g. space group and unit cell parameters.

It is noted that the claims do not require, and the specification does not describe, any common characteristics that define the structure of the instant proteins within the genus or of the genus of crystals as a whole. In general, for a species of crystal to be adequately structurally described, the following must be effectively disclosed in the specification and *in the claims*: (1) the composition of the crystal (exact structural features of all molecules in the crystal must be described, including the protein (preferably a SEQ ID NO of all included residues) and any molecule bound to it), (2) the space group, and (3) the unit cell dimensions of the crystal. Alternatively, where the crystal is described by product-by-process, the crystal must be adequately described by reciting the exact and full conditions for crystallization (e.g. method, exact buffer, salt

and/or additive concentrations, pH, temperature) and the method claims must include the same in the same claim.

It is very well known in the art that a singular chemical composition can crystallize differently based on the crystallization conditions and the protein to be crystallized (e.g. variants, mutants, homologs, derivatives, etc. – also see scope of enablement rejection above), and the space group and unit cell dimensions of a crystal of any given chemical composition can only be determined by analyzing that crystal's X-ray diffraction (Giege *et al.* Crystallogenesis of Biological Macromolecules: Facts and Perspectives. Acta Cryst., (1994) D50: 339-350 –cited previously). However, based on the instant specification, the chemical composition, space group, and unit cell dimensions and methods of making thereof encompassed by the representative genus of the claims, is unpredictable to one of skill in the art. While the three representative P-selectin LE crystal species noted above have adequately met the burden of being fully described in the specification and indeed are three species found within the genus, this is not sufficient to reflect the wide variability of protein structures and space groups and unit cell dimensional of the crystals. For a broad generic claim, the specification must provide adequate written description to identify the genus of the claim by describing a sufficient number of representative species. In *Regents of the University of California v. Eli Lilly & Co.* the court stated:

> "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *Fiers*, 984 F.2d at 1171, 25 USPQ2d 1601; *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 284985 (CCPA 1973) *("In other cases, particularly but not necessarily, chemical cases, where there is*

> *unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus ...*") *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

In addition, MPEP 2163 states, "when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus."

However, because the variability of the composition of crystals encompassed by the recited genus of the claims (e.g. an unlimited number or P-selectin LE proteins having as few as two contiguous amino acids SEQ ID Nos: 6, 8 or 9, with conservative substitutions thereof) and also the space groups and unit cell parameters of these variant crystals which are encompassed by the genus, is not be reflected by these three crystal species because of the extensive unpredictability in the art of crystallography (see Cudney et al., pp. 1-7, Drenth et al., Chapter 1, p. 19, 4th paragraph, lines 1-2; and McPherson et al., p. 13, recited above), then said species can not be considered to be representative of the entire genus. Therefore, claims drawn to the instant genera of P-selectin LE proteins contained within the crystals, nor the crystals themselves (e.g. crystal forms having different space groups) are not adequately described.

It is further noted, that even though new claims 61-65 attempt to limit claims 15 or 56 by reciting the specific space group and unit cell parameters (claim 61, 63 and 65), or the ligand of the crystals (claims 62 and 64), the claims still do not possess written description because the independent claims are unlimited as to the amino acid sequences used to make said crystals, particular in view of the broad by reasonable interpretation of the claims, which encompass P-selectin LE polypeptides have as few

as two consecutive amino acids of SEQ No: ID 6, 8, or 9, and those which also encompass conservative substitutions there of.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. The following excerpt is from MPEP § 2106 section VI "DETERMINE WHETHER THE CLAIMED INVENTION COMPLIES WITH 35 U.S.C. 102 AND 103" and is applied to the below 35 USC §103(a) rejection wherein the claimed limitations of "generating a three dimensional model of P-selectin LE using the relative structure coordinates of Figures 2, 3 and 5 ± 1.5Å" and "...wherein the active site comprises relative structural coordinates of amino acids ....." are considered "non-functional descriptive material".

> As is the case for inventions in any field of technology, assessment of a claimed computer-related invention for compliance with 35 U.S.C. 102 and 103 begins with a comparison of the claimed subject matter to what is known in the prior art. If no differences are found between the claimed invention and the prior art, the claimed invention lacks novelty and is to be rejected by Office personnel under 35 U.S.C. 102. Once distinctions are identified between the claimed invention and the prior art, those distinctions must be assessed and resolved in light of the knowledge possessed by a person of ordinary skill in the art. Against this backdrop, one must determine whether the invention would have been obvious at the time the invention was made. If not, the claimed invention satisfies 35 U.S.C. 103. Factors and considerations dictated by law governing 35 U.S.C. 103 apply without modification to computer-related inventions.

If the difference between the prior art and the claimed invention is limited to descriptive material stored on or employed by a machine, Office personnel must determine whether the descriptive material is functional descriptive material or nonfunctional descriptive material, as described supra in sections IV.B.1(a) and IV. B.1(b). Functional descriptive material is a limitation in the claim and must be considered and addressed in assessing patentability under 35 U.S.C. 103. Thus, a rejection of the claim as a whole under 35 U.S.C. 103 is inappropriate unless the functional descriptive material would have been suggested by the prior art. > In re Dembiczak, 175 F.3d 994, 1000, 50 USPQ2d 1614, 1618 (Fed. Cir. 1999).< Nonfunctional descriptive material cannot render nonobvious an invention that would have otherwise been obvious. Cf. In re Gulack, 703 F.2d 1381, 1385, 217 USPQ 401, 404 (Fed. Cir. 1983) (when descriptive material is not functionally related to the substrate, the descriptive material will not distinguish the invention from the prior art in terms of patentability).

Common situations involving nonfunctional descriptive material are:
- a computer-readable storage medium that differs from the prior art solely with respect to nonfunctional descriptive material, such as music or a literary work, encoded on the medium,

- a computer that differs from the prior art solely with respect to nonfunctional descriptive material that cannot alter how the machine functions (i.e., the descriptive material does not reconfigure the computer), or

- a process that differs from the prior art only with respect to nonfunctional descriptive material that cannot alter how the process steps are to be performed to achieve the utility of the invention.

Thus, if the prior art suggests storing a song on a disk, merely choosing a particular song to store on the disk would be presumed to be well within the level of ordinary skill in the art at the time the invention was made. The difference between the prior art and the claimed invention is simply a rearrangement of nonfunctional descriptive material.

9. Claims 66-69 are rejected under 35 U.S.C. 103(a) as being unpatentable over Revelle et al. (JBC, 1996, 271(27):16160-16170 – cited on the IDS from 10 December 2001) in view of Morris et al. (J. of Computer-Aided Molecular Design. 1996. Vol. 10, pp. 293-304 – cited previously on PTO-892 of 7-3-06) in view of *In re Gulack* 217 USPQ 401 (Fed. Cir. 1983) and *In re Ngai* 70 USPQ2d 1862 (Fed. Cir. 2004). See MPEP §§

2144 and 2144.04 regarding legal precedent as a source of rationale for rejection under 35 U.S.C. § 103.

All claim limitations concerning the machine readable data comprising structure coordinate data of Figures 2, 3 and 5 are given no patentable weight as it is considered to be non-functional descriptive material. As such, the instant claims are considered to be limited to a method of using a known computer program to identify agents that interact with P-selectin by inputing the three-dimensional structural coordinates into said computer program, and analyzing the output by visual/mental interpretation.

Revelle et al. teach that E-selectin and P-selectin are two closely related vascular cell adhesion proteins, each with a lectin type domain that binds carbohydrates and a EGF-like domain (see first two lines of Abstract). Revelle et al. also teach site directed mutataions of both proteins leading to structural and functional insights to the mode of action of selectins. Exactly how the mutations actually lead to their role in the disruption of selectin activity is unclear. It is specifically stated, that it seems likely that only the three-dimensional structure (NMR or protein crystallography) will be able to elucidate the mechanism of action of the selectins. Furthermore, "the presented data do offer new insight into selectin/ligand interactions and perhaps identify the necessity for further structural and functional analyses of those interactions and their modulation. It is hope that this information will aid in the design and identification of high affinity selectin inhibitors that may be used for the treatment of selectin-mediated inflammatory disease." (see p. 16170, 1st column, last four sentences). Revelle et al. do not,

however, teach the three-dimensional structure or the *in silico* design and identification of inhibitors of P-selectin.

Morris et al. sets forth a software program developed for designing and determining the potential ligand-protein interactions based on known protein structures (AutoDock). The program aids the skilled artisan in determining if a protein ligand specifically interacts with the known protein structure and how well/likely said interaction actually is. The user interface requires that the skilled artisan provide the three-dimensional structure file (also known as the .pdb file) as determined by X-ray crystallographic, solution NMR spectroscopy or other known means. The disclosed program includes a full description of an advanced software system specifically for performing simulated annealing and rigid body refinement of the protein with the potential bound ligand. The program thus gives a more accurate analysis of the energy minimum/maximum calculations required for 'real world' ligand-protein interaction (e.g. the likely-hood of ligand interacting in a non-static protein) [see Introduction, p. 293]. It is taught on p. 293, 2nd column, 1st full paragraph, that the program has been used successfully in the prediction of substrates binding to enzymes and computer-aided drug design of non-peptide inhibitors as well as other applications. The suite of software for AutoDock quite simply can be manipulated by different commands by the user in order to produce the results desired so long as the protein structure is known.

Revelle et al. teach why a skilled artisan would be motivated to investigate the interaction of ligands with either P-selectin or E-selectin: because the design and identification of high affinity selectin inhibitors may be used for the treatment of selectin-

mediated inflammatory disease. Morris et al. teach a computer program that specifically is used with structural coordinates/data that are fed into a known algorithm whereby the program identifies interactions between the structural coordinates and a known or designed ligand. The computer program uses a series of pre-defined processing steps in order to identify the interaction and the data which is input into the program do not intrinsically impose a change to those processing steps and are thus the data is nonfunctional descriptive material. In *Gulack* and *Ngai*, the respective Courts held that nonfunctional descriptive material cannot render nonobvious an invention that would have otherwise been obvious. In the instant case, a method of using a known computer program (such as those listed on p. 23 of the specification or that of Morris et al.) for its known and intended purpose to compare data and ligand interaction does not become nonobvious merely because new structural data becomes available for analysis.

Therefore it would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains to utilize the program AutoDock (developed by Morris et al.) which is specifically used for identifying agents/ligands that interact with macromolecular structures and to use said program with any three-dimensional structural coordinates, including those of the instant claims/invention.

Response to Arguments

10. Applicant's arguments filed 25 May 2007 have been fully considered but they are not persuasive.

35 U.S.C. 112 – 1st Scope of Enablement:

11. The examiner has maintained the rejection of claims 15, 16, 36-60 and added new claims 61-69.

Applicants assert that in view of the newly amended claims, which specifies that P-selectin LE sequence used in the crystals is either SEQ ID No: 6, 8, or 9, or conservative substitutions thereof, that the aspect of the previous Office action's rejection regarding that the claims are unlimited in the number and variance of different P-selectin LE proteins used to make the crystals, is now moot (see Remarks, p. 12). Applicants further note that the claims now encompass "conservative substitutions of SEQ ID No: 6, 8 or 9" and reiterate how it is defined in the specification on p. 16, lines 7-20.

> Thus, the term "conservative substitutions" refers to those substitutions that have a requisite polarity, steric arrangement and/or belonging to the same class of substituted residue, such that the substituted residues remain within the root mean square deviation from the backbone atoms of P-selectin LE having the structural coordinates specified, i.e., no more than anywhere between 0.5 to 1.5 Å.
>
> Moreover, newly added claims 61-65, which depend from independent claims 15 and 56, recite a particular group symmetry and unit parameter dimension of the crystals from which the structural coordinates are obtained. Thus, the claims, as amended or newly added herein, are no longer directed to "any particular specific protein sequence and thus would encompass any and every fragment, derivative or homolog of any of these P-selectin LE proteins," but to methods for identifying agents that interact with P-selectin LE having the amino acid sequence specified, or conservative substitutions thereof, using three dimensional models generated using either the full structural coordinates according to Figures 2, 3 or 5, or the selected residues specified, ± a root mean square deviation from the backbone atoms of P-selectin LE of not more than 1.5A.

However, this is unconvincing. First it is noted that the proteins of the recited crystal are not limited to SEQ ID No: 6, 8 or 9, or conservative variants thereof, in view of the broad interpretation of the claims as noted above. Instead, the scope of proteins that the crystal encompasses is P-selectin proteins having any two contiguous amino acids of SEQ ID No: 6, 8 or 9, or those that have conservative substitutions thereof. Second, even conservative substitutions can have enormous consequences in terms of a protein actually crystallizing and it is wholly unpredictable which ones might be tolerated and which will not. As noted above, McPherson makes this point that even changes as few as one or two amino acids can have large consequences. Applicants assert that the claims are no longer drawn to any or all protein variants of P-selectin but to methods of identifying agents that interact with P-selectin LE having the amino acid sequence specified, or conservative substitutions thereof. However, the claims are, in fact, still drawn to many different crystals of P-selectin LE, which is a definitive part of the claim limitations because one is required to provide a crystal then obtain relative structural information therefrom. It is noted that the latter half of the claim actually is in no way dependent upon, however, the crystals of the claim because, for instance, in claim 15, once one has obtained the relative structural coordinates of the crystallized P-selectin LE, which notably can be derived from many different crystals, the relative structural coordinates from said crystal are not actually used in the method or required to be used in the method(s), rather the coordinates of Figures 2, 3 and 5 are used. It is in no way apparent or limiting that the structural coordinates from the crystal are one and the same as the structural coordinates of said relative structural coordinates of said

Figures 2, 3 or 5. Thus, while the claims are still drawn to *in silico* methods, the claims clearly use crystal and obtain structural information, albeit for what purpose is not clear from the claim.

Applicants further suggest that they have provided ample examples of crystal forms and relative structural coordinates of "P-selectin structural coordinates in complexed and free form so as to enable one of ordinary skill in the art to design and/or identify agents that interact with the P-selectin sequences recited in the claims. More specifically, the structural coordinates of human P-selectin in uncomplexed form and complexed with two different ligands, i.e., SLeX and PSGL-1, are disclosed in the specification in Figures 2, 3 or 5, respectively." (see Remarks, p. 5). Applicants also assert that the prior art and the specification disclose what is well known about P-selectins regarding important amino acids regarding the location, interactions of various residues, and the domains of the P-selectin LE, and how all of these residues correlate to biological activity and/or binding to its receptor. It is stated: "Therefore, at the time the present application was filed, one of ordinary skill in the art would have known to make changes (e.g., conservative substitutions) to human P-selectin LE within the level of deviation required by the claims without undue experimentation." (see Remarks, p. 13). While this might be true for proteins that are soluble and require a biological activity, this says absolutely nothing about the effects that these particular amino acids have on crystallization and whether or not conservative substitutions will have a significant impact of reproducibility of the protein crystals. Applicants also argue that high resolution crystallography and molecular modeling techniques are extensively

described in the instant application, and were known in the art at the time the application was filed. Soft-ware systems for generating three-dimensional models were also described in the specification, and were known in the art. Thus, one of ordinary skill in the art would have been able to generate P-selectin LE three dimensional models having the sequence specified or conserved variants thereof by practicing routine experimentation. The Examiner acknowledges this later point, but again, the point at issue is the conservative substitutions of the proteins that are used to make the protein crystals, *not* three-dimensional structures derived from the crystals. These sorts of substitutions will not preclude the protein from crystallizing because obviously they occur *in silico*. The Examiner, however, is pointing out the unpredictability of even conservative substitutions on crystallization.

Applicants further maintain that the references relied upon by the Examiner to establish unpredictability in fact do the opposite. Applicants focus in on the tediousness and time consuming constraints of setting up crystallization trials and state:

> As to the unpredictability of the crystallography art raised by the Examiner, it is acknowledged that establishing adequate protein crystallization conditions is a tedious and time-consuming process. However, this does not mandate a conclusion that the experimentation required for such process is necessarily undue as set forth by the enablement standard in Wands (858 F.2d 731) and re-articulated in the Falkner decision (448 F. 3d at 1365). Automated methods for speeding up "the tedious work of reproducibly setting up large numbers of crystallization experiments" were known in the art at the time the application was filed. See e.g., Branden and Tooze, "Introduction to Protein Structure," Second edition, Garland Publishing Inc., New York (1999) at page 375. Methods of producing pure and homogeneous protein samples successful for crystallization can be readily obtained using recombinant techniques, Id. Even the crystallographic phase is characterized by Flower (2002) Drug Design, Cutting Edge Approaches, Royal Society of Chemistry. However, even the recalcitrant discipline [crystallography phase] is yielding to the power of robotics and

> bioinformatics [citation omitted]. This allows many more trials to be performed and at much more accurately defined conditions than is the case for manual crystallizations. This has, in turn, led to the successful crystallization of many seemingly intractable proteins, such as several subunits from the lipocalin crustacyanin. Others have used sophisticated statistical techniques to speed the search for crystallization conditions but cutting down the number of conditions that needed to be tested. For example, robust multivariate statistics has been used to relate variations in experimental condition, within experimentally designed crystallization trials, to their results [citation omitted]. Although these mathematical models cannot explain crystallization mechanisms, they do provide a powerful pragmatic tool allowing the setting up of crystallization trials in a more rational and more confident manner, particular when proteins are in limited supply. Flower reference at page 23.

The question here is not how much or whether or not robotics have assisted in easing the tediousness and time-consuming constraints of protein crystallization experiments. Rather, analysis of the enablement requirement is not based upon how much experimentation is required, which seems to be what Applicants are arguing (e.g. the quantity is eased by the advent of the latest technology), but rather the enablement requirement hinges upon whether or not undue experimentation is required. According to MPEP 2164.01(a), "There are many factors to be considered in determining whether undue experimentation is required." The Examiner is asserting that undue experimentation is required, whether using robotics or not, in part because the predictability of crystallizing proteins is exceptionally erratic. Cudney et al. and Drenth et al. (both cited previously) are examples of how luck plays a role in an extremely complex and confounding science, e.g. crystallizing proteins. Nonetheless, and contrary to Applicants assertions regarding robotics, while assisting greatly in the art of protein crystallography, said robotics does nothing for the unpredictability of the science. This is well known and well acknowledged in the art today. For instance,

Kundrot et al. (Kundrot, C.E., Cellular Molecular Life Science. 2004. Vol., 61, pp. 525-536) state the following :

> The three-dimensional, atomic-resolution protein structures produced by X-ray crystallography over the past 50+ years have led to tremendous chemical understanding of fundamental biochemical processes. The pace of discovery in protein crystallography has increased greatly with advances in molecular biology, crystallization techniques, cryocrystallography, area detectors, synchrotrons and computing. While the methods used to produce single, well-ordered crystals have also evolved over the years in response to increased understanding and advancing technology, ***crystallization strategies continue to be rooted in trial-and-error approaches***.

It is noted that Kundrot et al. was published well after Applicants effective filing date. Thus, even with robotics assisting in the amount of experimentation required, said experimentation is still merely trial-and-error and thus unpredictable. The Examiner disagrees with the assertion that the references cited actually support the Branden et al. and Flowers et al. assertions (it is noted that Branden et al. and Flowers et al. are not references relied upon by the Examiner, nor are they art of record (Branden et al. was cited previously, p. 249 and is of record, however, Applicants arguments are drawn to p. 345 and has not been provided)) and that the instant case is supported by the Falkner et al. decision. Again, the rejection is not based solely upon amount of experimentation required, rather, it is bases on all relevant factors of *In re Wands*, particularly the unpredictability of the experimentation expected and required. If in a science it is routine to find unexpected results that hinge on unexplained phenomena, for example, the air conditioner breaking down in the laboratory where the crystallization experiments have been set-up, so that the resulting temperature in the lab is raised so as to unexpectedly, unpredictably and luckily be raised to just the right temperature to enable

crystal growth (see Drenth et al., p 19, 4th paragraph, lines 1-2), or wherein crystals will grow only if the person setting up the crystallization experiments holds the test tube containing the protein in their hand, rather than placing said test-tube back on ice in between each individual experiment (see Cudney, see p. 2-3, especially, p.3), then this is not considered to be an exact science, rather it is sketchy, unreliable and an unpredictable science which will mandate undue experimentation given the scope of Applicants claims. As noted, it is a science riddled with unexplained phenomena, wherein changing the tiniest thing, e.g. conservative amino acid substitutions, may have enormous consequences.

Written Description:

The Examiner has maintained the rejection of claims 15, 16, 36-60 and new claims 61-69 as lacking written description.

Applicants assert the following:

> To expedite prosecution of the instant application, the claims, as amended or newly added herein, are directed to methods for identifying agents that interact with P-selectin LE having the amino acid sequence specified (i.e., amino acid sequence of SEQ ID NO:6, 8 or 9, or conservative substitutions thereof), using three dimensional models generated using the full structural coordinates according to Figures 2, 3 or 5, or the selected residues specified, ± a root mean square deviation from the backbone atoms of P-selectin LE of not more than 1.5A. Thus, the pending claims are no longer directed to "a large number of species of P-selectin crystals containing P-selectin proteins from any species and which are derivatives, homologues or fragments thereof," and thus obviate this aspect of the rejection."

However, the Examiner disagrees with these assertions and purports that the claims are still drawn to a large variable genus with regard to both the proteins and the crystal forms. Furthermore, Applicants seem to mischaracterize their own claim by omitting

that the claims actually are limited to "providing a crystal comprising P-selecting LE wherein the P-selectin LE comprises an amino acid sequence of SEQ ID No: 6, 8 or 9, or conservative substitutions thereof;". The claims, as written, are not drawn to methods of identifying agents that interact with P-selectin LE having the amino acid sequence specified (i.e., amino acid sequence of SEQ ID NO:6, 8 or 8, or conservative substitutions thereof), rather the *in silico* methods portion of claims only require Figures 2, 3, or 5. As noted above, the later half of the claim actually is in no way dependent upon the crystals of the claim because, for instance, in claim 15, once one has obtained the relative structural coordinates of the crystallized P-selectin LE, which can be one of many different crystals as noted, the relative structural coordinates from said crystal are not actually used in the method, rather the coordinates of Figures 2, 3 and 5 are used. It is in no way apparent or no way limiting that the structural coordinates from the crystals are one and the same as the relative structural coordinates of said Figures 2, 3 or 5. In fact, assuming one did make a protein crystal of P-selectin LE of SEQ ID No: 6 (for example) which did have any number of conservative substitutions, then the relative structural coordinates of Figures 2, 3 or 5 would be not be the same as the relative structural coordinates derived from the new crystal, and it is unknown if they would be within the given rmsd. Applicants finally assert that with regards to the Examiner's assertions of the high level of unpredictability in the art, their position as noted above for the scope of enablement is reiterated. It is thus, reestablished that *de novo* crystallization conditions would not be necessary because the method requires the use of the relative structural coordinates of Figures 2, 3 or 5. However, as noted above, the

claims are directed to providing various crystals before using the relative structural coordinates of Figures 2, 3 or 5, and it is the crystals which belong to a large genus of proteins contained within the crystal, as well as a large genus of different crystal forms, e.g. space groups, because the claim does not require the use of the structural coordinates derived from said crystals. Nonetheless, the claim still encompasses said crystals, which encompasses various proteins therein and various crystal forms. Since Applicants have provided only two species of proteins used in crystallizations which resulted in 3 crystal form species, it is deemed these are not representative of the wide variation within the genus.

Conclusion

12. No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Suzanne M. Noakes, Ph.D. whose telephone number is 571-272-2924. The examiner can normally be reached on Monday to Friday, 7.00am to 3.30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr Bragdon can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

SMN
06 June 2007

Susan M. Noakes
Examiner AU 1656